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HELLER EHRMAN WHITE & MCAULIFFE LLP
1666 K STREET,NW
SUITE 300
WASHINGTON, DC 20006

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/214,913	SMITH ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 53-84 are pending.

2. In view of the amendment filed 9/11/03, the following rejections remain.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 53-55, 57-58, and 62-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Sigal *et al*, (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892).

Sigal *et al* teach a membrane targeting agent such (Myr-GSSKSKPKDPSQRRR) wherein the reference agent consisting of a myristoyl group (Myr) which is a lipophilic binding element consisting of aliphatic acyl group (12 methylene units) linked to a hydrophilic amino acid sequence rich with positively charged residues such as lysine and arginine (GSSKSKPKDPSQRRR) and a linker such as a peptide bond that binds to a molecule or membrane component such as a phosphatidylcholine/phosphatidylserine (artificial membrane) (See page 12253, column 1, in particular). The reference membrane localization reagent contains at least five basic residues such as lysine. The term "comprising" is open-ended. It expands the hydrophilic peptide binding elements to include additional amino acid to read on the reference peptide binding element. Claims 62-63 are included in this rejection because the reference lipophilic binding element myristic acid contains 12 methylene units, which are within the claimed 8 to 18 or 10 to 14 methylene units. Sigal *et al* teach that a peptide containing both the myristoyl group (Myr) and the positively charged lysine residues can enhance the binding of the soluble polypeptide to the membrane because the hydrophilic and electrostatic binding energy are additive (see page 12253, column 2, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Sigal use synthetic peptides to compete for Src binding to vesicles, but they did not employ such peptide to mediate such binding in soluble proteins. There is no teaching of how to achieve post-translational modification or any suggestion of how to achieve it in practice. (2) The Src is an intracellular protein that does not normally exist in a soluble form outside the cell. And there is no teaching that directs modification of proteins in an extracellular environment.

In response, the term "post-translational modification" is not recited in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). See MPEP 2145. Further, synthetic vesicles are outer membrane. In considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01. Finally, the term "comprising" or "comprises" is open-ended. It expands the lipophilic binding element such as aliphatic acyl groups and the hydrophilic peptide binding element to include additional undisclosed functional group and/or amino acids at either or both ends.

5. Claims 53-59, 62-63, and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by Hancock *et al* (EMBO J 10(13): 4033-9, Dec 1991; PTO 892).

Hancock *et al* teach a membrane targeting agent such as a lipophilic peptide binding element comprising aliphatic acyl group such as palmitoyl (14 methylene units), farnesyl or geranylgeranyl, a hydrophilic peptide binding element such as basic amino acids such as six lysine or six arginine and a linker such as a bond that links the reference hydrophilic element to a molecule such as p21K-ras(B) (see abstract, in particular). Hancock *et al* teach polyarginine domain can function as a plasma membrane targeting motif and replacing the polyarginine domain with the polylysine domain is still biological active (See abstract, in particular). The term "comprising" is open-ended. It expands the lipophilic peptide binding element to include additional carbon at either end to read on the reference farnesyl or geranylgeranyl of the lipophilic peptide binding element. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that Hancock et al also describe the structural features associated with intracellular proteins that can undergo reversible interaction with the inner membrane leaflet. Handcock et al do indeed establish that inner membrane binding in the p21kRas and Src proteins is mediated by a combination of electrostatic and hydrophobic effects. However, Hancock et al do not teach how to make and apply membrane localizing reagents. Further, Hancock also reports that methyesterification is required for efficient membrane binding, which is not required in the present invention.

In response, methyesterification merely enhances the efficiency of membrane binding. Further, the term comprising is open-ended. It expands the claimed membrane localization reagent to include additional functional group to read on the reference membrane localization reagent.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 53, 67, 68-70, 72-73, 77-78 and 80-81 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al* (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) in view of Citro *et al* (Dis Colon Rectum 37(2): 127-32, abstract, Feb 1994; PTO 892). The teachings of Sigal *et al* have been discussed supra.

The claimed invention as recited in claim 67 differs from the teachings of the reference only that the membrane localization reagent wherein the molecule is a therapeutic agent.

The claimed invention as recited in claim 68 differs from the teachings of the reference only that the soluble compound that is directed to an outer membrane of a cell comprises a therapeutic agent, a membrane localization wherein the membrane localization reagent is soluble and comprises (a) lipophilic binding element comprising aliphatic acyl groups; (b) a hydrophilic peptide binding element comprising basic amino acids, wherein the hydrophilic binding element is bound to the lipophilic element and (c) a linker that covalently binds the therapeutic agent to the hydrophilic peptide binding element of the membrane localization reagent from the soluble compound.

The claimed invention as recited in claim 69 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises lysine residues.

The claimed invention as recited in claim 70 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises three to ten lysine residues.

The claimed invention as recited in claim 72 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises arginine residues.

The claimed invention as recited in claim 73 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises three to ten arginine residues.

The claimed invention as recited in claim 77 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises 8 to 18 methylene units.

The claimed invention as recited in claim 78 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises 10 to 14 methylene units.

The claimed invention as recited in claim 80 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises myristoyl.

The claimed invention as recited in claim 81 differs from the teachings of the reference only that the soluble compound wherein the linker is a bond.

Citro *et al* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell.

The reference method of conjugating a drug such as c-myb antisense oligonucleotide to a ligand such as transferin, folic acid or steroid covalently linked to a polylysines through disulfide bridge (cysteine) and used as a carrier to direct the drug to the cell (See abstract, in particular). Citro *et al* teach the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the ligand such as transferrin as taught by Citro *et al* for the targeting agent such (Myr-GSSKSKPKDPSQRRR) wherein the reference agent consisting of a myristoyl group (Myr) which is a lipophilic binding element consisting of aliphatic acyl group (12 methylene units or 14 carbons) linked to a hydrophilic amino acid sequence rich with positively charged residues such as lysine and arginine (GSSKSKPKDPSQRRR) and a linker such as a cysteine disulfide peptide bond that binds to any drug for directing the drug to the outer membrane as taught by Citro *et al* and Sigal *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Citro *et al* teach the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

Applicants' arguments filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that Signal and Hancock discuss natural phenomena that occur inside the cell, whereas applicant's invention is an inventive approach for localizing molecules to the outside of cells at the outer membrane. There is no combined teaching in the references that would allow the skilled person achieve applicant's invention with a reasonable expectation of success.

However, the synthetic vesicle such as phosphatidylcholine/phosphatidylserine (artificial membrane) as taught by Signal et al is considered an outer membrane. Further, the use of hydrophilic peptide such as polylysines and aliphatic acyl group such as Myr-GSSKSKPKDPSQRRR through disulfide bridge (cysteine) to direct a cargo such as a drug or molecule to the outer membrane of a cell is not without precedence as taught by as taught by Citro *et al* and Sigal *et al.*

9. Claims 53, 67-74, 77-78 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hancock *et al* (EMBO J 10(13): 4033-9, Dec 1991; PTO 892) in view of Citro *et al* (Dis Colon Rectum 37(2): 127-32, abstract, Feb 1994; PTO 892).

The teachings of Hancock et al have been discussed supra.

The claimed invention as recited in claim 67 differs from the teachings of the reference only that the membrane localization reagent wherein the molecule is a therapeutic agent.

The claimed invention as recited in claim 68 differs from the teachings of the reference only that the soluble compound that is directed to an outer membrane of a cell comprises a therapeutic agent, a membrane localization wherein the membrane localization reagent is soluble and comprises (a) lipophilic binding element comprising aliphatic acyl groups; (b) a hydrophilic peptide binding element comprising basic amino acids, wherein the hydrophilic binding element is bound to the lipophilic element and (c) a linker that covalently binds the therapeutic agent to the hydrophilic peptide binding element of the membrane localization reagent from the soluble compound.

The claimed invention as recited in claim 69 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises lysine residues.

The claimed invention as recited in claim 70 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises three to ten lysine residues.

The claimed invention as recited in claim 71 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises four to seven lysine residues.

The claimed invention as recited in claim 72 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises arginine residues.

The claimed invention as recited in claim 73 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises three to ten arginine residues.

The claimed invention as recited in claim 74 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises four to seven arginine residues.

The claimed invention as recited in claim 77 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises 8 to 18 methylene units.

The claimed invention as recited in claim 78 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises 10 to 14 methylene units.

The claimed invention as recited in claim 81 differs from the teachings of the reference only that the soluble compound wherein the linker is a bond or a cysteine residue.

Citro *et al* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell. The reference method of conjugating a drug such as c-myb antisense oligonucleotide to a ligand such as transferin, folic acid or steroid covalently linked to a polylysines through disulfide bridge (cysteine) and used as a carrier to direct the drug to the cell (See abstract, in particular). Citro *et al* teach that the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the ligand as taught by Citro *et al* for the targeting agent comprising the lipophilic peptide binding element such as the aliphatic acyl group of palmitoyl which has 14 methylene units or farnesyl or geranylgeranyl linked to a hydrophilic peptide binding element such as six basic amino acids from the group of lysine or arginine and a linker such as a peptide bond or disulfide bond via cysteine that links any drug for directing the drug to the outer membrane as taught by Citro *et al* and Sigal *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Citro *et al* teach that the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular). Hancock et al teach the key feature of polybasic domain in the CAAX or CAAL motif provides signal for plasma membrane targeting and the polybasic domain appears to be a positive charge replacing the polylysine domain with polyarginine still can function as a plasma membrane targeting domain motif (See abstract, in particular).

Applicants' arguments filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that Signal and Hancock discuss natural phenomena that occur inside the cell, whereas applicant's invention is an inventive approach for localizing molecules to the outside of cells at the outer membrane. There is no combined teaching in the references that would allow the skilled person achieve applicant's invention with a reasonable expectation of success.

However, the synthetic vesicle such as phosphatidylcholine/phosphatidylserine (artificial membrane) as taught by Signal et al is considered an outer membrane. Further, the use of hydrophilic peptide such as polylysines and aliphatic acyl group such as Myr-GSSKSKPKDPSQRRR through disulfide bridge (cysteine) to direct a cargo such as a drug or molecule to the outer membrane of a cell is not without precedence as taught by as taught by Citro *et al* and Sigal *et al.*

10. Claims 68 and 82-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al* (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) or Hancock *et al* (EMBO J 10(13): 4033-9, Dec 1991; PTO 892) each in view of US Pat No. 5,472,939, (of record, Dec 1995, PTO 892) and Citro *et al* (Dis Colon Rectum 37(2): 127-32, abstract, Feb 1994; PTO 892).

The teachings of Sigal *et al* and Hancock *et al* have been discussed supra.

The claimed invention of claim 82 differs from the teachings of the references only that the soluble compound wherein the therapeutic agent is a complement inhibitor.

The claimed invention of claim 83 differs from the teachings of the references only that the soluble compound wherein the therapeutic agent comprises Short Consensus Repeat 1-3 of Long Homologous Repeat A of Complement Receptor 1.

The claimed invention of claim 84 differs from the combined teachings of the references only that soluble derivative or a soluble polypeptide wherein the membrane component ligand consisting of a peptide containing between 3 and 14 amino acids derived known ligands for membrane components

The '939 patent teaches a soluble complement regulatory protein sCR1 which has a short consensus structure motif that binds to a complement component for reducing tissue damage associated with myocardial infarction (See column 8, lines 15-40, column 9, lines 29 and 43-44,

column 67, 68, 69 and Abstract, in particular). The '939 patent further teaches a fusion protein comprising a portion of the CR1 sequence plus a non-CR1 sequence (See column 21, lines 39-42). The '939 patent teach other deletion mutants of CR1 which are functional derivatives (See column 16, lines 41-58, in particular).

Citro *et al* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell. The reference method of conjugating a drug such as c-myb antisense oligonucleotide to a ligand such as transferin, folic acid or steroid covalently linked to a polylysines through disulfide bridge (cysteine) and used as a carrier to direct the drug to the cell (See abstract, in particular). Citro *et al* teach that the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently link the membrane localization reagent as taught by Sigal *et al* or Hancock *et al* with the soluble complement inhibitor or short consensus repeat 1-3 of Long Homologous Repeat A of Complementary Receptor 1 for directing said soluble complement inhibitor to the outer membrane of a cell as taught by Sigal *et al,* or Hancock *et al* to improve the therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular) as taught by Citro *et al*.

One having ordinary skill in the art would have been motivated to do this because the '939 patent teaches that a soluble CR1 molecule or fusion protein may be used to treat damage caused by a myocardial infarction associated with inflammation and inappropriate complement activation (See column 8, lines 15-40, column 9, lines 29 and 43-44, column 67, 68, 69 and Abstract, in particular). Sigal *et al* teach that a peptide containing both the myristoyl group (Myr) and the positively charged lysine residues can enhance the binding of the soluble polypeptide to the membrane because the hydrophilic and electrostatic binding energy are additive (see page 12253, column 2, in particular). Hancock *et al* teach that polyarginine domain can function as a plasma membrane targeting motif and replacing said polyarginine domain with the polylysine domain is still biological active (See abstract, in particular). Citro *et al* teach that the advantage of targeting delivery of any drugs would improve therapeutic index having maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular). Claim 84 is included in this rejection because the '939 patent teach the derivative of soluble complement regulatory protein sCR1 which has a short consensus structure motif that binds to a complement component

and CR1 is a known ligand (See column 16, lines 41-58, in particular).

Applicants' arguments filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that Signal and Hancock discuss natural phenomena that occur inside the cell, whereas applicant's invention is an inventive approach for localizing molecules to the outside of cells at the outer membrane. There is no combined teaching in the references that would allow the skilled person achieve applicant's invention with a reasonable expectation of success.

However, the synthetic vesicle such as phosphatidylcholine/phosphatidylserine (artificial membrane) as taught by Signal et al is considered an outer membrane. Further, the use of hydrophilic peptide such as polylysines and aliphatic acyl group such as Myr-GSSKSKPKDPSQRRR through disulfide bridge (cysteine) to direct a cargo such as a drug or molecule to the outer membrane of a cell is not without precedence as taught by as taught by Citro *et al* and Sigal *et al.*

11. Claims 68 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al* (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) or Hancock *et al* (EMBO J 10(13): 4033-9, Dec 1991; PTO 892) each in view of Citro *et al* (Dis Colon Rectum 37(2): 127-32, abstract, Feb 1994; PTO 892) and EP 0,207,589 A1, (Jan 1987, PTO 892) or EP 0,155,387 A2 (Sept 1985, PTO 892) or US Pat No 5,326,700 (July 1994, PTO 892).

The teachings of Sigal *et al* and Hancock *et al* have been discussed supra.

The claimed invention of claim 82 differs from the teachings of the references only that the soluble compound wherein the therapeutic agent is a tissue plasminogen activator, a prourokinase or streptokinase.

Citro *et al* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell. The reference method of conjugating a drug such as c-myb antisense oligonucleotide to a ligand such as transferin, folic acid or steroid covalently linked to a polylysines through disulfide bridge (cysteine) and used as a carrier to direct the drug to the cell (See abstract, in particular). Citro *et al* teach that the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

The EP 0207,589 A1 patent teaches tissue type plasminogen activator, functional derivatives thereof such as urokinase (see page 10, in particular) and pharmaceutical compositions for treatment of thrombotic diseases (See page 6, lines 39-42).

The EP 0,155,387 A2 patent teaches hybrids of plasmin linked to urokinase plasminogen activator B-chain (See page 11, claims 1-4 of EP 0,155,387 A2 and a pharmaceutical composition for treating thrombotic diseases (See pages 6-7, in particular).

The '700 patent teaches a tissue plasminogen activator having an amino acid sequence identical to SEQ ID NO: 22 of the instant application (See column 39, SEQ ID NO: 16 of '700, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently link the membrane binding elements as taught by Sigal *et al* or Hancock *et al* with the tissue type plasminogen activator, or functional derivatives thereof such as urokinase as taught by the EP 0207,589 A1 patent or the hybrids of plasmin linked to urokinase plasminogen activator B-chain as taught by the EP 0,155,387 A2 patent or the tissue plasminogen activator as taught by the '700 patent for directing said soluble complement inhibitor to an outer membrane of a cell as taught by Sigal *et al,* Hancock *et al* to improve therapeutic index by having maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular) as taught by Citro *et al.*

One having ordinary skill in the art would have been motivated to do this because the the tissue type plasminogen activator, or functional derivatives thereof and hybrid as taught by the EP 0207,589 A1 patent or the EP 0,155,387 A2 patent or the plasminogen activator as taught by the '700 patent can be used for treating thrombotic disease. Citro *et al* teach that the advantage of targeting delivery of any drugs would improve therapeutic index having maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular). Sigal *et al* teach that a peptide containing both the myristoyl group (Myr) and the positively charged lysine residues can enhance the binding of the soluble polypeptide to the membrane because the hydrophilic and electrostatic binding energy are additive (see page 12253, column 2, in particular). Hancock *et al* teach that the polyarginine domain can function as a plasma membrane targeting motif and replacing the polyarginine domain with the polylysine domain is still biological active (See abstract, in particular).

Applicants' arguments filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that Signal and Hancock discuss natural phenomena that occur inside the cell, whereas applicant's invention is an inventive approach for localizing molecules to the outside of cells at the outer membrane. There is no combined teaching in the references that would allow the skilled person achieve applicant's invention with a reasonable expectation of success.

However, the synthetic vesicle such as phosphatidylcholine/phosphatidylserine (artificial membrane) as taught by Signal et al is considered an outer membrane. Further, the use of hydrophilic peptide such as polylysines and aliphatic acyl group such as Myr-GSSKSKPKDPSQRRR through disulfide bridge (cysteine) to direct a cargo such as a drug or molecule to the outer membrane of a cell is not without precedence as taught by as taught by Citro *et al* and Sigal *et al.*

12. Claims 53, 66, 68 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al*, (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) or Hancock *et al* (EMBO J 10(13): 4033-9, Dec 1991; PTO 892) each in view of EP 0109,653 (May 1984; PTO 892) or EP 0152736 (of record, Aug 1985, PTO 892).

The teachings of Sigal *et al* and Hancock *et al* have been discussed supra.

The claimed invention of claims 66 and 81 differs from the teachings of the references only that the soluble compound or therapeutic agent wherein the linker is a cysteine residue, an amide at the C-terminus, a haloacetyl group where halo signifies chlorine, bromine or idodine or an ε amino acid group of a lysine residue.

Citro *et al* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell. The reference method of conjugating a drug such as c-myb antisense oligonucleotide to a ligand such as transferin, folic acid or steroid covalently linked to a polylysines through disulfide bridge (cysteine) and used as a carrier to direct the drug to the cell (See abstract, in particular). Citro *et al* teach the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

The EP 0152736 patent teaches various linker such as a N-haloacetyl group where halo signifies chlorine, bromine or idodine for preparing various urokinase complex which is useful as a thrombolytic agent (page 17, line 10, abstract, in particular)

The EP 0152736 patent teaches an enzyme-protein conjugate using bridging groups having a formula of (I): -A-R-B- in which each of A and B, which may be the same or different, represents -CO-, -C(=NH2+)-, maleimido group which contains a cysteine, a sulfahydryl group such as -S-, or a bond and R is a bond or a linking group containing one or more -(CH2)- or meta-, ortho- or para- disubstituted phenyl units optionally together with a hydrophobic portion; the R is selected from -(CH2)r-, -(CH2)p-S-S-(CH2)q- (See pages 2-3, 31, in particular). The EP 0152736 patent further teaches the enzyme-protein conjugates made using the method mentioned above are suitable as a pharmaceutical composition (See page 11, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the linker as taught by Sigal *et al* or Hancock *et al* for the N-haloacetyl group as taught by the EP 0152736 patent or the cysteine maleimido group as taught by the EP 0152736 patent for directing the soluble compound or therapeutic agent to the outer membrane as taught by Citro *et al*, Sigal *et al* and Hancock *et al.*

One having ordinary skill in the art would have been motivated to use the bridging group as taught by the EP 0152736 patent because the derivative or conjugates made using these bridging group are suitable for pharmaceutical compositions (See page 11, in particular). The EP 0152736 patent teaches various linker such as a N-haloacetyl group where halo signifies chlorine, bromine or idodine for preparing various urokinase complex which is useful as a thrombolytic agent (page 17, line 10, abstract, in particular).

Applicants' arguments filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that Signal and Hancock discuss natural phenomena that occur inside the cell, whereas applicant's invention is an inventive approach for localizing molecules to the outside of cells at the outer membrane. There is no combined teaching in the references that would allow the skilled person achieve applicant's invention with a reasonable expectation of success.

However, the synthetic vesicle such as phosphatidylcholine/phosphatidylserine (artificial membrane) as taught by Signal et al is considered an outer membrane. Further, the use of hydrophilic peptide such as polylysines and aliphatic acyl group such as Myr-GSSKSKPKDPSQRRR through disulfide bridge (cysteine) to direct a cargo such as a drug or molecule to the outer membrane of a cell is not without precedence as taught by as taught by Citro *et al* and Sigal *et al.*

13. The following new ground of objection and rejections are necessitated by the amendment filed 9/11/03.

14. Claim 68 is objected to because part (b) is missing.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 53-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (A) a membrane localization reagent for directing a molecule to an outer membrane of a cell selected from the group consisting of SEQ ID NO: 37-41, wherein the membrane localization reagent is soluble and comprises (1) a lipophilic binding element consisting of aliphatic acyl group wherein the aliphatic acyl group is myristoyl group, (2) a hydrophilic peptide binding element consisting of basic amino acids selected from the group consisting of lysine or arginine bound to the lipophilic element and (3) a linker for covalently binding the molecule to the hydrophilic peptide binding element of the membrane localization reagent, (B) the said membrane localization reagent wherein the hydrophilic peptide binding element consisting of three to ten or four to seven residues such as lysine or arginine, (C) the said membrane localization reagent wherein the lipoprotein binding element consisting of 8 to 18 or 10 to 14 methylene units such as myristyoyl, (D) the said membrane localization reagent wherein the linker is selected from the group consisting of a cysteine residue; an N-haloacetyl group wherein the halo is selected from the group consisting of chlorine, bromine, or iodine, a haloacetyl group wherein the halo is selected from the group consisting of chlorine, bromine, or iodine at an ε-amino group of a lysine residue, an amide group at the C-terminus, and a fatty acid N-acyl group at the N-terminus or at an ε-amino group of a lysine residue wherein the fatty acid is myristoyl, (E) the said membrane localization reagent wherein the molecule is a therapeutic agent selected from the group consisting of a specific antibody such as CD4, B7/CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein kinase C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, urokinase, and streptokinase for directing said therapeutic agent to the outer membrane of a cell, (F) A soluble compound that is directed to an

outer membrane of a cell wherein the soluble compound consisting of (1) a therapeutic agent and (2) a membrane localization reagent selected from the group consisting of SEQ ID NO: 37-41, wherein the membrane localization reagent is soluble and comprises a lipophilic binding element consisting of aliphatic acyl group wherein the aliphatic acyl group is a myristoyl group, a hydrophilic peptide binding element consisting of basic amino acids selected from the group consisting of lysine or arginine bound to the lipophilic element, a linker for covalently binding the therapeutic agent to the hydrophilic peptide binding element of the membrane localization reagent, and (4) wherein the therapeutic agent is selected from the group consisting of a specific antibody such as CD4, B7/CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein kinase C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, urokinase, and streptokinase for directing said therapeutic agent to the outer membrane of a cell, **does not** reasonably provide enablement for *any* membrane localization reagent as set forth in claims 53-59, 62-67 and *any* soluble compound that is directed to an outer membrane of a cell as set forth in claims 68-83 and any soluble derivative of any soluble polypeptide as set forth in claim 84 for directing *any* molecule, any therapeutic agent such as the ones recited in claims 82-83 for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a membrane localizing reagent consisting of only two heterologous membrane binding elements wherein one of the membrane binding elements is a myristoyl fatty acid with 12 methylene units and a basic polylysine amino acid sequence selected from the group consisting of GSSKSPSKKKKKKPGD, DGPKKKKKKSPSKSSG, SPSNETPKKKKKKRFSFKKSG, DGPKKKKKKSPSKSSK, SKDGKKKKKKSKTK,

DGPKKKKKKSPSKSSGC, GSSKSPSKKKKKKPGDC, CDGPKKKKKKSPSKSSK, or SKDGKKKKKKSKTKC which is covalently associated with a soluble complement receptor (SCR1-3) (SEQ ID NOS: 7-14 and 17), or a conjugate of Streptokinase (SEQ ID NO: 21), or a plasminogen activator (SEQ ID NO: 22) for **in vitro assays** such as inhibition of complement-mediated lysis (pages 50-52), plasminogen activator assay (page 53) and erythrocyte binding assays (See pages 54-57).

The specification does not teach how to make and use *any* membrane localization reagent comprises *any* lipophilic binding element "**comprising**" *any* aliphatic acyl groups, *any* hydrophilic peptide binding element "**comprising**" basic amino acids, and a linker for binding *any* "molecule" to the hydrophilic peptide binding element of the membrane localization reagent because the term "comprising" is open-ended. It expands the "aliphatic acyl group" to include infinite number of carbon and undisclosed functional groups at either or both ends, it also expands the "hydrophilic binding elements" to include infinite number of undisclosed amino acids at either or both ends in addition to the basic amino acids that are already in the hydrophilic binding element of the localization reagent. There is insufficient guidance as to the structure of the membrane localizing reagent, let alone having the same function as the hydrophilic peptide SEQ ID NO: 37-41 such as directing any molecule or therapeutic agent to an outer membrane of a cell. It is noted that none of the disclosed hydrophilic peptides of SEQ ID NO: 37-41 have more than ten basic amino acid residues. The term "comprises" in claims 54-61, 68-74 extends the peptide binding element to include additional basic amino acid residues to include additional amino acid at either or both ends. There is insufficient guidance whether the resulting structure having extra amino acids such as hydrophobic amino acids would have the same function as the hydropyhilic peptides of SEQ ID NO: 37-41. Since the structure of the hydrophilic peptide element within the membrane localizing reagent is not enable, it follows that any hydrophilic peptide element "comprises" lysine or arginine residues such as three to ten or four to seven are not enabled. Likewise, the term "comprises" in claims 62-65, and 68-80 extends that lipophilic binding element, and the hydrophilic peptide to include additional functional group in addition to the indicated methylene units. There is insufficient guidance as to which undisclosed additional functional group to be added and whether the resulting structure has the same function as the lipophilic binding element for directing the therapeutic agent to the outer membrane of a cell, in turn, useful for treating a specific disease.

It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama *et al* teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* teach further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet *et al* teach that a single Glu to Val substitution in the subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, paragraph bridging columns in particular). Thus, knowing structure alone will not inherently tell us function (See figure, entire document). As such, further research would be required. Since the lipophilic binding element within the membrane localizing reagent are not enable, it follows that any peptide element such as the ones recited in claims 60-61 are not enable. It also follows that any lipophilic binding element "comprises" methylene units such as 8 to 18, 10 to14 or myristoyl group are not enabled.

With regard to claim 66, there is insufficient guidance as to the structure and function of any "N-terminal blocking group", any "bond", any "fatty acid N-acyl group" at the N terminus or at an ε-amino group of a lysine residue for linking any molecule to the hydrophilic peptide binding element. Further, because the undisclosed "blocking group" at the N-terminus is used as blocking, it is not clear why one would link any molecule to the blocking group. Given the indefinite number of undisclosed membrane localization reagent having undisclosed N-terminal blocking group and fatty acyl group, there is insufficient working example demonstrating *any* undisclosed membrane localization reagent is effective for directing a molecule to an outer membrane of a cell. It is unpredictable which undisclosed membrane localization reagent would direct any molecule to an outer membrane of a cell for treating any disease.

With regard to any soluble compound that is directed to an outer membrane of a cell comprising any therapeutic agent, *any* membrane localizing reagent mentioned above, not only the membrane localizing reagent and linker mentioned above are not enabled, the term "therapeutic agent" encompasses indefinite number of undisclosed "therapeutic agent" that may

not have an effect when directed to the cell membrane. The specification merely discloses only a specific antibody such as CD4, B7/CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, urokinase, and streptokinase for directing said therapeutic agent to the outer membrane of a cell, much less for treating any disease. Given the indefinite number of therapeutic agent, there is insufficient working example in the specification as filed. It is unpredictable which undisclosed therapeutic agent comprising any undisclosed therapeutic agent linked to any membrane localizing agent comprising the undisclosed hydrophilic binding element and the undisclosed lipophilic binding element and linker would effectively targeting the therapeutic agent to the cell membrane for treating any disease. In the absence of sufficient guidance as how to extrapolate data obtained from in vitro assays to the development of effective therapeutic agent direct to the outer membrane of a cell in vivo for treating any disease commensurate in scope with the claimed invention, it is not clear that the skilled artisan could predict the efficacy of the soluble compounds exemplified in the specification for in vivo treatment of any disease encompassed by the claims.

With regard to claims 82, the claim encompasses any antibody, any complement inhibitor, and any tissue plasminogen activator, there is insufficient guidance as to the binding specificity of any antibody, much less directing said antibody to the outer-membrane of any cell by linking to any undisclosed membrane localization reagent mentioned above. Other than the specific antibody, the specific complement inhibitor and the specific tissue plasminogen activator, there is insufficient guidance as to the structure of any complement inhibitor and any tissue plasminogen activator mentioned above, let alone having the same function as the specific complement inhibitor or plasminogen activator for treating all disease.

With regard to claim 83, the term "comprises" is open-ended. It expands the short consensus repeats 1-3 of long homologous Repeat A of complement receptor 1 to include additional amino acid at either or both ends of said repeat. There is insufficient guidance as to the structure of the undisclosed additional amino acid to be added, much less having the same function. Even if the term "comprising" is changed to "consisting of", the term Short Consensus Repeats 1-3 of Long Homologous Repeat A of complement receptor 1 without SEQ ID NO has no structure. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the

structure of any "short consensus repeats 1-3 of Long Homologous Repeat A of complement receptor 1", any "lipophilic binding element, any "hydrophilic peptide binding element", any "therapeutic agent", any "soluble compound", and still provide or maintain sufficient targeting specificity to an outer membrane of a cell for treating any disease is unpredictable and the experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue.

With regard to claim 84, the terms "derivative", "soluble polypeptide" without the specific amino acid sequence have no structure. Further, there is insufficient guidance as to which two or more non identical heterologous membrane binding elements when linked to which undisclosed soluble polypeptide is capable of interacting with which undisclosed "components" of cellular or artificial membranes. Further, there is insufficient guidance as to the structure of any derivative of soluble polypeptide such as membrane component ligand further consisting of any peptide containing between 3 to 13 undisclosed amino acids derived from transmembrane proteins identified by screening of chemical, bacteriophage or displayed libraries. Given the indefinite number of undisclosed soluble polypeptide derivative, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the objective of this invention is to provide for membrane localization of therapeutic agents through the inventive insight that a synthetic combination of low-affinity membrane ligands combined with a linker group can provide an affinity for cell membrane while maintaining solubility. The linkage of the specified reagents to direct "cargo" (therapeutics" is independent of the nature of the cargo and such concept is not without

precedence. (2) Mikayma and Voet studies are not relevant to instant invention because the invention does not require any of the membrane interactive components to have any specific 3D structure.

However, the structure of the membrane localization reagent such as the lipophilic binding element that linked to the hydrophilic peptide for directing any cargo such as molecule and therapeutics to an outer membrane of a cell is not defined. Further, the term "comprising" or "comprises" is open-ended. It expands the lipophilic binding element such as aliphatic acyl groups and the hydrophilic peptide binding element to include additional undisclosed functional group and/or amino acids at either or both ends. There is insufficient guidance as to which undisclosed lipophilic binding element and the hydrophilic peptide binding element to be added and whether the resulting membrane localization reagent would maintain solubility and concomitantly provide affinity for cell membrane to direct the cargo or therapeutics to the outer membrane. Further, there is insufficient working example to demonstrate that *any* undisclosed membrane localization reagent comprising any lipophilic binding element, any hydrophilic peptide binding element, linker and any soluble compound or any therapeutic agent would be effective for treating any disease such as rheumatoid arthritis or complement mediated disease. Further, there is insufficient guidance as to the structure of any derivative of soluble polypeptide such as membrane component ligand further consisting of any peptide containing between 3 to 13 undisclosed amino acids derived from transmembrane proteins identified by screening of chemical, bacteriophage or displayed libraries. Given the indefinite number of undisclosed soluble polypeptide derivative, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

17. Claims 53-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* membrane localization reagent as set forth in claims 53-59, 62-67 and *any* soluble compound that is directed to an outer membrane of a cell as set forth in claims 68-83 and any soluble derivative of any soluble polypeptide as set forth in claim 84 for directing *any* molecule, any therapeutic agent such as the ones recited in claims 82-83 for treating *any* disease.

With the exception of the specific membrane localization reagent such as SEQ ID NO: 37-41 linked to the therapeutic agent such as a specific antibody such as CD4, B7/CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, an urokinase, a streptokinase for directing said therapeutic agent to the outer membrane of a cell for the corresponding disease, there is inadequate written description about the structure associated with function of *any* membrane localization reagent comprises *any* lipophilic binding element "comprising" *any* aliphatic acyl groups, *any* hydrophilic peptide binding element "comprising" basic amino acids, and a linker for binding *any* "molecule" to the hydrophilic peptide binding element of the membrane localization reagent because the term "comprising" is open-ended. It expands the "aliphatic acyl group" to include infinite number of carbon or functional groups at either or both ends, it also expands the "hydrophilic binding elements" to include infinite number of undisclosed amino acids at either or both ends in addition to the basic amino acids that are already in the hydrophilic peptide binding element of the localization reagent. Since the hydrophilic peptide element within the membrane localizing reagent are not adequately described, it follows that any hydrophilic peptide element "comprises" lysine or arginine residues such as three to ten or four to seven are not adequately described. It follows that any peptide element such as the ones recited in claims 60-61 are not adequately described. It also follows that any lipophilic binding element "comprises" methylene units such as 8 to 18, 10 to 14 or a myristoyl group is not adequately described.

With regard to claim 66, there is insufficient written description about the structure and function of any "N-terminal blocking group", any "bond", any "fatty acid N-acyl group" at the N terminus or at an ε-amino group of a lysine residue for linking any molecule to the hydrophilic

peptide binding element. Further, the "blocking group" at the N-terminus is used for blocking; it is not clear why one would link any molecule to the blocking group.

With regard to any soluble compound that is directed to an outer membrane of a cell comprising any therapeutic agent, any membrane localizing reagent mentioned above, not only the membrane localizing reagent and linker mentioned above are not adequately described, the term "therapeutic agent" encompasses indefinite number of undisclosed "therapeutic agent" that may not have the same effect when directed to the cell membrane, let alone for treating any disease. The specification discloses only a specific antibody such as CD4, B7/CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, urokinase, and streptokinase for directing said therapeutic agent to the outer membrane of a cell. Given the indefinite number of soluble compound, there is insufficient written description about the structure and function of any undisclosed therapeutic agent, in turn, linked to any membrane localizing agent comprising the undisclosed hydrophilic binding element and the undisclosed lipophilic binding element and linker would effectively targeting the therapeutic agent to the cell membrane for treating any disease.

With regard to claims 82, the claim encompasses any antibody, any complement inhibitor, any tissue plasminogen activator, there is insufficient written description about the binding specificity of any antibody, much less directing said antibody to the outer-membrane of any cell by linking to any undisclosed any membrane localization reagent mentioned above. Other than the specific antibody, the specific complement inhibitor and the specific tissue plasminogen activator, there is insufficient written description about the structure of any complement inhibitor and any tissue plasminogen activator, let alone having the same function as the specific complement inhibitor or plasminogen activator for treating any disease.

With regard to claim 83, the term "comprises" is open-ended. It expands the short consensus repeats 1-3 of long homologous Repeat A of complement receptor 1 to include additional amino acid at either or both ends of said repeat. There is inadequately written description about the structure of the undisclosed additional amino acid, much less having the same function. Even if the term "comprising" is changed to "consisting of", the term Short Consensus Repeats 1-3 of Long Homologous Repeat A of complement receptor 1 without SEQ ID NO has no structure.

With the exception of the specific membrane localization reagent such as SEQ ID NO: 37-41 and the specific soluble compound comprising the specific therapeutic agent linked to the specific membrane localization reagent mentioned above, there is inadequate written description of *any* additional representative species of membrane localization reagent, lipophilic binding element, hydrophilic peptide binding element, linker and soluble compound, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

With regard to claim 84, the terms "derivative", "soluble polypeptide" without the specific amino acid sequence have no structure. Further, there is inadequate written description about which two or more non identical heterologous membrane binding elements when linked to which undisclosed soluble polypeptide is capable of interacting with which undisclosed "components" of cellular or artificial membranes. Further, Given the indefinite number of undisclosed soluble polypeptide derivative, the structure of any derivative of soluble polypeptide such as membrane component ligand further consisting of any peptide containing between 3 to 13 undisclosed amino acids derived from transmembrane proteins identified by screening of chemical, bacteriophage or displayed libraries is not adequately described. Applicant is directed to the Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the objective of this invention is to provide for membrane localization of therapeutic agents through the inventive insight that a synthetic combination of low-affinity membrane ligands combined with a linker group can provide an affinity for cell membrane while maintaining solubility. The linkage of the specified reagents to direct "cargo" (therapeutics" is independent of the nature of the cargo and such concept is not without precedence. (2) Mikayma and Voet studies are not relevant to instant invention because the invention does not require any of the membrane interactive components to have any specific 3D structure.

However, the structure of the membrane localization reagent such as the lipophilic binding element that linked to the hydrophilic peptide for directing any cargo such as molecule

and therapeutics to an outer membrane of a cell is not defined. Further, the term "comprising" or "comprises" is open-ended. It expands the lipophilic binding element such as aliphatic acyl groups and the hydrophilic peptide binding element to include additional undisclosed functional group and/or amino acids at either or both ends. There is inadequate written description about the structure associated with function as to which undisclosed lipophilic binding element and the hydrophilic peptide binding element to be added and whether the resulting membrane localization reagent would maintain solubility and concomitantly provide affinity for cell membrane to direct the cargo or therapeutics to the outer membrane. Further, there is inadequate written description about *any* undisclosed membrane localization reagent comprising any lipophilic binding element, any hydrophilic peptide binding element, linker and any soluble compound or any therapeutic agent would be effective for treating any disease such as rheumatoid arthritis or complement mediated disease. Further, given the lack of guidance as to the structure of any derivative of soluble polypeptide such as membrane component ligand further consisting of any peptide containing between 3 to 13 undisclosed amino acids derived from transmembrane proteins identified by screening of chemical, bacteriophage or displayed libraries, the soluble derivative of any undisclosed soluble polypeptide is not adequately described. With the exception of the specific membrane localization reagent such as SEQ ID NO: 37-41 and the specific soluble compound comprising the specific therapeutic agent linked to the specific membrane localization reagent mentioned above, there is a lack of a written description of *any* additional representative species of membrane localization reagent, lipophilic binding element, hydrophilic peptide binding element, linker and soluble compound, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

19. Claim 84 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

22. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
December 15, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600